

Twenty-four-week effects of liraglutide on body composition, adherence to appetite, and lipid profile in overweight and obese patients with type 2 diabetes mellitus

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Background: Liraglutide has well-known effects on glucose patterns. However, its several other metabolic properties are still controversial. Given this background, the aims of the present study are to evaluate the effects of 24-week liraglutide treatment on body composition, appetite, and lipid profile in overweight and obese type 2 diabetes mellitus (T2DM) patients.

Methods: A cohort study was carried out on overweight and obese T2DM patients with glycosylated hemoglobin A_{1c} equal to 6% (42 mmol/mol)–10% (86 mmol/mol), under a 3-month treatment (at least) with maximal dose of metformin as stable regime, by adding liraglutide at doses up to 3 mg/d. Body composition markers were measured by dual-energy X-ray densitometry at baseline and after 24 weeks of liraglutide treatment. Glucose control was monitored by glucose, glycosylated hemoglobin A_{1c}, insulin, and homeostasis model assessment. Finally, the appetite sensation and plasma lipids were also evaluated.

Results: Twenty-eight subjects (male/female: 16/12, mean age: 58.75±9.33 years, body mass index: 34.13±5.46 kg/m²) were evaluated. Accounting for the adjustment for age, sex, and duration of diabetes, we noted significant decreases in body mass index (−0.86 kg/m², *P*=0.024), fat mass (−2.01 kg, *P*=0.015), fat mass index (−0.71 kg/m², *P*=0.014), android fat (−1.72%, *P*=0.022), trunk fat (−1.52%, *P*=0.016), and waist circumference (−6.86 cm, *P*<0.001) from the baseline values. Haber score was increased by 3.82 units (*P*=0.009), and the number of metabolic syndrome risk factors was decreased (−0.69 units, *P*=0.012). The glucose control variables and total cholesterol/high-density lipoprotein cholesterol ratio also showed significant decreases from baseline values.

Conclusion: The 24-week liraglutide treatment leads to the reduction of fat mass, android fat, trunk fat, and appetite by improving the lipid profile, glucose control, and insulin sensitivity.

Keywords: liraglutide, weight loss, body composition, fat mass, type 2 diabetes mellitus, appetite

Background

The World Health Organization estimated that 2.3 billion adults would be overweight and that more than 700 million would be obese by 2015; this is largely due to dietary and other lifestyle factors.¹ The incidence of type 2 diabetes mellitus (T2DM) and insulin resistance (IR) are associated with obesity. In particular, T2DM is closely linked to “android obesity”, characterized by abdominal visceral fat accumulation.^{2,3} In addition, morbid obesity, dyslipidemia, and hypertension place T2DM patients at strong risk of cardiovascular (CVD) disease, related to morbidity and mortality.⁴

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In this sense, it is necessary to develop an effective and efficient therapeutic target strategy for both T2DM and obesity. Liraglutide, a glucagon-like peptide-1 (GLP-1) analog, is a member of the new classes of antidiabetic agents, and it is characterized by its ability to induce insulin secretion only during hyperglycemia (as an incretin effect).⁵

Liraglutide has the ability to decrease blood glucose without causing hypoglycemia, and, at the same time, it has several other metabolic properties: 1) promoting and maintaining a substantial weight loss;⁶⁻⁸ 2) deceleration of the gastric emptying; and 3) inducing satiety, decreasing energy intake.^{9,10}

Niswender et al¹¹ investigated the weight change in subjects with T2DM treated with liraglutide compared to those treated with other diabetes therapies. They showed that the weight loss was greater in subjects treated with GLP-1 receptor than those in the active comparator-treated group.

However, the various metabolic activities of liraglutide in addition to glycemic control are still controversial. In particular, few studies evaluated the body composition changes associated with weight loss in liraglutide-treated subjects, by correlating with appetite sensation and other metabolic alterations.

Given this background, the primary aim of this study was to assess the effect of the 24-week liraglutide treatment, at doses up to 3 mg/d, on body composition in overweight and obese individuals with T2DM. Liraglutide treatment effects on appetite sensation, lipid profile, and IR were also investigated as secondary objectives.

Methods

Study participants

The cohort study was performed following the approval of the Ethics Committee of the Department of Internal Medicine and Medical Therapy of the University of Pavia. Written informed consent was obtained from all patients for participation in the study.

We evaluated white male and female subjects with T2DM admitted to the outpatient setting of the Agency for Elderly People Services, Santa Margherita Hospital in Pavia, between September 2012 and June 2014.

The inclusion criteria were: 1) overweight or obese subjects (body mass index [BMI] ≥ 25 kg/m²); 2) glycosylated hemoglobin A_{1c} (HbA_{1c}) = 6% (42 mmol/mol)–10% (86 mmol/mol); 3) metformin treatment at maximal dose and stable regime since 3 months (at least); 4) liraglutide treatment initiated at 1.2 mg once daily, titrated to 3 mg once daily after 1 week; 5) duration of diabetes between 1 and 19 years; and 6) subjects ≥ 18 years of age.

Body composition, nutritional status and food intake

Body composition was measured by dual-energy X-ray densitometry (DXA) using a Lunar Prodigy DXA (GE Medical Systems, Waukesha, WI, USA). The *in vivo* coefficients of variation were 0.89% and 0.48% for fat and muscle mass, respectively. Fat mass and muscle mass were evaluated by whole body scan. Fat mass index (FMI) was derived as fat mass (kg) divided by the square of the height (m²), and free fat mass index (FFMI) as free fat mass (kg) divided by the square of the height (m²). The relative skeletal muscle mass was derived as the sum of fat-free soft tissue mass of arms and legs, as described by Janssen et al.¹²

Body weight was measured to the nearest 0.1 kg by using a precision scale, with the subjects wearing light clothing and without shoes, using standardized technique.¹³

BMI and waist circumference were also calculated.

Patients ate five meals daily: breakfast between 7 and 8 am, a snack between 10 and 10.30 am, lunch between 12 am and 2 pm, a snack between 4 and 4.30 pm, and dinner between 7 and 8 pm. Individual diet plans were drawn up for each subject by the research dietitian. The energy content and macronutrient composition of the diets adhered to the nutritional recommendations of the American Diabetes Association.^{14,15}

To optimize compliance, dietary instructions were reinforced weekly by the same research dietitian. Each consultation included a nutritional assessment and weighing. A 3-day weighed-food record of 2 weekdays and 1 weekend day was prepared before the study and during the last week of intervention. Individual diet plans and dietary records were analyzed using a food-nutrient database (Rational Diet, Milan, Italy).

Rating of appetite

Visual analog scales were used to assess appetite sensations. Satiety was numerically assessed using a scoring system graded from –10, to represent extreme hunger, to +10, to represent extreme satiety. The scale with 21 graduations, characterized by items that describe the various degrees of hunger or satiety, was shown to all subjects. They were free to choose any point along the scale in relation to their hunger or satiety sensations. The point chosen was defined as the Haber score.¹⁶

Biochemical analyses

Blood samples were obtained from subjects in the fasted state before and after 6-month liraglutide treatment. The blood samples were taken, immediately cooled and centrifuged at 4°C, and then stored at –80°C until analysis.

HbA_{1c} was analyzed using a high-performance liquid chromatography, ion-exchange chromatography assay (HLC-723G7, TOSOH, Tokyo, Japan). Serum concentrations of insulin and C-peptide were analyzed by enzyme-linked immunosorbent assay methods. Serum glucose, lipid profiles, and liver biochemistry were determined by using the Hitachi 7070 automatic biochemical analyzer (Hitachi Ltd, Tokyo, Japan).

A_{1c}-derived average glucose (ADAG) was calculated.¹⁷ IR was evaluated by the homeostasis model assessment (HOMA),¹⁸ using the following formula: HOMA-IR = ([fasting insulin, µU/mL] × [plasma glucose, mmol/L])/22.5.

Definition of metabolic syndrome

The metabolic syndrome (MetS) was identified based on The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III).¹⁹

Statistical analysis

Data were expressed as mean ± standard deviation. Linear mixed models (LMM) for repeated measures²⁰ were applied in order to assess the differences in blood, body composition and appetite sensation variables, among individuals at pre- and post-treatment (post – pre). These data were presented as mean differences with 95% confidence intervals. Nonnormally distributed data were checked by Shapiro–Wilk test and log-transformed for parametric statistics. Therefore, for each outcome, we fit an LMM where age, sex, duration of diabetes, and time (pre =0, post =1) were the explanatory variables. A random effect was used to adjust the models for intrasubject variability products by two different measurements carried out on the same patients (n=28, ×2=56 observations, but only 28 independents). The time LMM parameters were interpreted as adjusted mean changes (Δ-changes) from baseline (t₀). We carried out two-tailed *t*-tests (and 95% confidence interval) to evaluate statistical significance on model parameters. *P*-values <0.05 were considered significant. Thus, a Pearson correlation analysis was used to assess the pairwise relationships among the Δ-changes in body composition markers, and with Δ-changes in glucose control variables, lipid profile, and Haber score. The analysis was performed on R 2.15.3 using the R/nlme²¹ and R/stats packages (R Foundation for Statistical Computing, Vienna, Austria).²²

Results

Table 1 lists the baseline characteristics of the 28 subjects (male: 16, female: 12) at admission. The mean age was 58.75±9.33 years, the mean BMI was 34.13±5.46 kg/m²,

Table 1 Baseline (t₀) descriptive statistics of the sample

Variables	Total =28 (women: 12; men: 16) Mean ± SD
Age (years)	58.75±9.33
Body composition and muscle markers	
Height (m)	1.66±0.09
Body weight (kg)	94.58±18.32
BMI (kg/m ²)	34.13±5.46
Waist circumference (cm)	116.7±10.37
Total tissue (kg)	91.50±17.98
Fat mass (kg)	35.80±10.88
Free fat mass (kg)	55.70±10.84
Fat mass (%) on total tissue	38.63±7.23
FMI (kg/m ²)	13.01±4.14
FFMI (kg/m ²)	20.01±2.51
Af (%)	46.75±6.94
Gf (%)	39.49±9.09
Af/Gf ratio (units)	1.23±0.25
Tf (%)	42.39±6.54
Lf (%)	34.98±10.50
Arms fat (%)	37.30±10.79
Lif (%)	36.07±10.29
Tf/Lf ratio (units)	1.29±0.34
Tf/Lif ratio (units)	1.24±0.32
RSMM (kg/m ²)	8.76±1.22
Serum creatinine (mg/dL)	0.84±0.237
Glucose control variables	
Duration of diabetes (years)	6.52±5.55
Blood glucose level (mmol/L)	9.85±3.49
ADAG (mmol/L)	10.57±2.40
HbA _{1c} (%) (mmol/mol)	8.26 (67)±1.51
Insulin (mU/L)	17.11±11.23
HOMA (units)	7.88±6.39
C-peptide (ng/mL)	3.15±1.89
Lipid profile	
Triglycerides (mmol/L)	1.93±1.06
Cholesterol (mmol/L)	5.23±1.14
HDL (mmol/L)	1.20±0.37
LDL (mmol/L)	3.13±0.90
Cholesterol/HDL (units)	4.71±1.73
LDL/HDL (units)	2.82±1.20
Metabolic syndrome-related variables	
SBP (mmHg)	142.6±22.66
DBP (mmHg)	85.23±9.32
Number of metabolic syndrome risk factors	3.54±1.10
Metabolic syndrome (%)	89.3
Appetite sensation marker	
Haber score (units)	−0.88±6.90

Note: ^aLimbs = arms and legs.

Abbreviations: SD, standard deviation; BMI, body mass index; FMI, fat mass index (fat mass [kg]/height² [m²]); FFMI, free fat mass index (free fat mass [kg]/height² [m²]); Af, android fat; Gf, gynoid fat; Tf, trunk fat; Lf, legs fat; Lif, limbs fat; RSMM, relative skeletal muscle mass; ADAG, A_{1c}-derived average glucose; HbA_{1c}, glycosylated hemoglobin A_{1c}; HOMA, homeostasis model assessment; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

while the mean of the FMI and FFMI were 13.01 ± 4.14 and 20.01 ± 2.51 kg/m², respectively. Considering the lipid profile, the mean triglycerides was 1.93 ± 1.06 mmol/L and the mean total cholesterol was 5.23 ± 1.14 mmol/L. The average values of android to gynoid fat ratio (1.23 ± 0.25 units), glycated hemoglobin ($\text{HbA}_{1c} = 8.2\%$ [66 mmol/mol] $\pm 1.5\%$),

and ADAG (10.57 ± 2.40 mmol/L) indicated that the enrolled subjects had severe abdominal obesity and poor glycemic control. The baseline prevalence of MetS was 89.3%.

Table 2 lists, for all the outcomes, mean changes from baseline values, by LMM analysis, adjusting for age, sex, and duration of diabetes. There were significant reductions

Table 2 Linear mixed models

Variables	Mean changes from baseline ($t_1 - t_0$)	P-value	95% CI
Body composition and muscle markers			
Body weight (kg)	-2.45	0.026	-4.58; -0.31
BMI (kg/m ²)	-0.86	0.024	-1.60; -0.12
Waist circumference (cm)	-6.86	<0.001	-9.45; -4.27
Total tissue (kg)	-2.40	0.028	-4.51; -0.28
Fat mass (kg)	-2.01	0.015	-3.60; -0.43
Free fat mass (kg)	-0.39	0.403	-1.32; 0.55
Fat mass (%) on total tissue	-1.45	0.009	-2.51; -0.39
FMI (kg/m ²)	-0.71	0.014	-1.27; -0.15
FFMI (kg/m ²)	-0.13	0.407	-0.46; 0.19
Af (%)	-1.72	0.022	-3.17; -0.26
Gf (%)	-1.27	0.070	-2.66; 0.11
Af/Gf ratio (units)	-0.01	0.701	-0.05; 0.03
Tf (%)	-1.52	0.016	-2.74; -0.31
Lf (%)	-0.73	0.136	-1.69; 0.24
Arms fat (%)	-1.96	0.007	-3.33; -0.59
Lif ^a (%)	-1.10	0.185	-2.77; 0.56
Tf/Lf ratio (units)	-0.03	0.140	-0.06; 0.01
Tf/Lif ratio (units)	-0.02	0.571	-0.08; 0.04
RSM ^a (kg/m ²)	0.07	0.570	-0.18; 0.31
Serum creatinine (mg/dL)	-0.03	0.458	-0.10; 0.05
Glucose control variables			
Blood glucose level (mmol/L)	-2.92	<0.001	-4.19; -1.66
ADAG (mmol/L)	-2.23	<0.001	-3.15; -1.31
HbA _{1c} (%)	-1.40	<0.001	-1.98; -0.82
Insulin (mU/L)	0.51	0.916	-8.97; 9.98
HOMA (units) ^b	-0.43	0.031	-0.81; -0.06
C-peptide (ng/mL) ^b	0.12	0.630	-0.37; 0.61
Lipid profile			
Triglycerides ^b (mmol/L)	-0.26	0.069	-0.53; 0.02
Cholesterol (mmol/L)	-0.60	0.075	-1.28; 0.07
HDL (mmol/L)	0.07	0.314	-0.08; 0.21
LDL (mmol/L)	-0.23	0.391	-0.79; 0.33
Cholesterol/HDL (units) ^b	-0.20	0.020	-0.37; -0.04
LDL/HDL (units) ^b	-0.20	0.072	-0.42; 0.02
MetS-related variables			
SBP (mmHg)	-8.14	0.081	-17.40; 1.12
DBP (mmHg)	-4.20	0.150	-10.04; 1.65
Number of MetS risk factors	-0.69	0.012	-1.20; -0.17
Metabolic syndrome (%)	^c	^c	^c
Appetite sensation marker			
Haber score (units)	3.82	0.009	1.09; 6.56

Notes: The statistically significant evidences ($P < 0.05$) are in bold. ^aLimbs = arms and legs. ^bLog-transformed variables. ^cPoor stratum frequencies: the generalized LMM did not converge.

Abbreviations: CI, confidence interval; BMI, body mass index; FMI, fat mass index (fat mass [kg]/height² [m²]); FFMI, free fat mass index (free fat mass [kg]/height² [m²]); Af, android fat; Gf, gynoid fat; Tf, trunk fat; Lf, legs fat; Lif, limbs fat; RSM^a, relative skeletal muscle mass; ADAG, A1c-derived average glucose; HbA_{1c}, glycosylated hemoglobin A_{1c}; HOMA, homeostasis model assessment; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MetS, metabolic syndrome.

from baseline. Concerning the changes of body composition markers, significant decreases were found in body weight (-2.45 kg, $P=0.026$), BMI (-0.86 kg/m², $P=0.024$), and total tissue (-2.40 kg, $P=0.028$). Fat mass and FMI were significantly reduced by 2.01 kg ($P=0.015$) and 0.71 kg/m² ($P=0.014$) from baseline. Free fat mass and FFMI were also decreased by 0.39 kg and 0.13 kg/m², but these were not significant ($P=0.403$ and $P=0.407$). Average percentage of fat mass on tissue was decreased by 1.45% ($P=0.009$). In addition, android fat, trunk fat, and waist circumference decreased by 1.72% ($P=0.022$), 1.52% ($P=0.016$), and 6.86 cm ($P<0.001$), respectively.

Contextually, Haber score was increased by 3.82 units ($P=0.009$) and the number of MetS risk factors was averagely decreased (-0.69 unit, $P=0.012$). Also glucose control variables, such as blood glucose level (mmol/L), ADAG (mmol/L), HbA_{1c} (%), and log-HOMA (log[units]), showed significant decreases from baseline values, by 2.92 mmol/L ($P<0.001$), 2.23 mmol/L ($P<0.001$), 1.40% ($P<0.001$), and 0.43 log(units) ($P=0.031$), respectively.

Finally, concerning biochemical markers, total cholesterol-high-density lipoprotein cholesterol ratio (log) showed a significant decrease (-0.20 log[units], $P=0.020$). In addition, cholesterol (-0.60 mmol/L, $P=0.075$), triglycerides (-0.26 log[mmol/L], $P=0.069$), and low-density lipoprotein (LDL)-high-density lipoprotein (HDL) ratio (-0.20 log[units], $P=0.072$) showed suggestive but not significant evidences ($0.05<P<0.10$) of negative variations.

Regarding Pearson correlation analysis of the Δ -changes (t_1-t_0) in body composition and muscle markers, except waist circumference, a number of indicators were significantly correlated (the Pearson correlation equal to 0.37 is the cutoff that returns a $P=0.05$ from a two-sided test with sample size of the current study, $n=28$). It is to be noted that the correlations between FMI and total mass and tissue markers, ie, BMI (0.90 , $P<0.001$) and total tissue (0.90 , $P<0.001$) are higher than analog correlations with FFMI (0.70 , $P<0.001$ in both cases). In particular, total tissue changes were significantly correlated with gynoid fat (0.71 , $P<0.001$), leg fat (0.54 , $P=0.003$), android fat (0.49 , $P=0.009$), and trunk fat (0.48 , $P=0.009$).

Finally, concerning the correlations with the Δ changes of the glucose control variables, lipid profile, and Haber score, the latter showed a significant and inverse correlations with gynoid fat (-0.42 , $P=0.026$) and leg fat (-0.45 , $P=0.016$), while HbA_{1c} showed a positive correlation with waist circumference (0.42 , $P=0.026$) and negative correlations with android fat (-0.39 , $P=0.039$) and android/gynoid fat ratio (-0.42 , $P=0.026$).

Discussion

This study shows that the treatment with liraglutide (3 mg) over 24 weeks helps patients obtain good glycemic control (HbA_{1c} $=-1.40\%$, ADAG $=-2.23$ mmol/L, HOMA $=-0.43$ log[units]) and leads to a mean weight loss of 2.45 kg, specifically in fat mass (-2.01 kg and -0.71 kg/m²), android fat (-1.72%) and trunk fat (-1.52%), in Italian overweight and obese T2DM patients. Another interesting finding is related to the variation of the lipid profile, with the significant decrease of total cholesterol-HDL cholesterol ratio (-0.20 log[units]). Notably, changes in plasma levels of total cholesterol (-0.60 mmol/L) and triglycerides (-0.26 log[mmol/L]) were almost significant ($0.05<P<0.10$).

After 24 weeks of liraglutide therapy, a significant decrease of 1.40% in HbA_{1c} from baseline was detected. This is a good result when compared with other studies where the HbA_{1c} reductions were 0.8% , 0.33% , and 0.77% , respectively.^{23–25} Considering that in our study the patients had medium-high baseline HbA_{1c}, the decrease obtained is important for the metabolic control of the disease. This result was partially expected, because liraglutide, a GLP-1 analog, is a member of the newest class of T2DM therapies currently available, which improves hyperglycemia by increasing insulin secretion and reducing glucagon secretion.²⁶

The most important result of this study is the confirmation that the weight loss caused by liraglutide is primarily originated from reduction in fat mass rather than lean tissue mass. As a matter of fact, in our study, we found a significant decrease in fat mass and fat mass index (2.01 kg and 0.71 kg/m², respectively), android fat (1.72%), and trunk fat (1.52%). Furthermore, we might hypothesize that the reduction of abdominal visceral fat tissues is greater than that of subcutaneous fat tissues, as already demonstrated by Jendle et al,²⁷ Inoue et al,²⁸ Nauck et al,²⁹ and Li et al.³⁰

Previous studies have shown that liraglutide treatment produced sustained improvements in glycemic control, with a concomitant sustained weight loss.^{25,29,31–33} Nowadays, only few studies have evaluated the body composition by dual-energy X-ray absorptiometry,^{27–30} as was done in our study. Hence, it is interesting to go beyond the assessment of weight and studying the body composition (fat mass, muscle mass, and distribution of fat mass) of these patients, also considering the risk of CVD and its correlation with android fat. Therefore, liraglutide might be a promising new agent for the treatment of T2DM and abdominal obesity linked to high risk of CVD.

It is important to note that the weight loss and changes in body composition obtained in this study were not consciously

wanted by patients, who did not also follow a low-calorie diet. Customized nutritional advice, but not a low-calorie diet, was given to the patients. Furthermore, the subjects were all sedentary and did not change their lifestyle during the research. Finally, it is necessary to consider the ethnic background. Our study confirms the major results in terms of weight loss and adiposity performed on Asian subjects.³⁰

Thus, the unplanned weight loss achieved during the study has been probably due to the decrease of appetite sensation, as already demonstrated in previous studies:^{32,34,35} Haber score is significantly increased by 3.82 units. However, the mechanism involved in the action of GLP-1 in controlling appetite and body weight is still unknown.³⁶

Moreover, GLP-1 induces deceleration of gastric emptying and its anorexic actions appear to be mediated by the direct activation of the GLP-1 receptor in the central nervous system. GLP-1 also promotes the activation of the vagal nerve.^{37,38}

Concerning the interpretation of the lipid profile data, the beneficial effects of liraglutide treatment were also demonstrated in lipid metabolism disorders.^{32,39–41} In accordance with those previous studies, we observed that the treatment with liraglutide significantly improved CVD risk factors, including total cholesterol/HDL cholesterol ratio, but not triglycerides and LDL cholesterol.

Other studies found that LDL cholesterol level was significantly reduced at 6 and 12 months, while HDL cholesterol tended to increase.⁴² For these reasons, the treatment effect of liraglutide on the lipid profile should be further studied in depth.

Furthermore, in our study, we demonstrated that the number of factors identified by ATP III MetS significantly decreased.

Finally, another important key factor is the mean age of the subjects. In this regard, our study had a sample with age (58.75±9.33 years) greater than the age of sample subjects in other previous studies.

Overall, liraglutide was well tolerated and no safety concerns were identified. Occasionally, gastrointestinal disorders (nausea mainly) of mild severity were reported in two patients.

Concerning the limitations of the study, what can be the potential confounders of this study? It is possible that liraglutide is more effective in obese than in overweight or normal subjects, and in men compared to women. Accounting for this, we did not carry out a stratified analysis, but we just included adjustment covariates as sex, age and duration of diabetes.

Conclusion

In conclusion, 24-week treatment with 3 mg liraglutide is safe, well tolerated, and facilitates fat mass loss. In particular, it decreases the android and trunk fat and it improves lipid profile and glucose control in patients with T2DM. Our data support the rationale of other studies that investigated GLP-1 analogs in overweight and obesity patients having T2DM and dyslipidemia.

Disclosure

The authors report no conflicts of interest in this work.

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